



Obesity: epidemiology and clinical aspects

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At the beginning of the 21st Century, obesity has become the leading metabolic disease in the World. So much so, that the World Health Organisation refers to obesity as the global epidemic. In fact, obesity is a common disease affecting not only affluent societies but also developing countries. Currently 300 million people can be considered as obese and, due to the rising trend in obesity prevalence, this figure could double by year 2025 if no action is taken against this threat. In terms of health impairment, the importance of obesity lies in the fact that, besides being a disease in itself, it is a risk for many other diseases, mainly from the metabolic and cardiovascular area. Among these, type 2 diabetes, dyslipemia, hiperuricemia, arterial hypertension and cardiovascular disease are the most frequent. Also, respiratory diseases such as obesity hypoventilation syndrome and obstructive sleep apnoea syndrome are strongly associated with obesity.

Key words: obesity; epidemiology; arterial hypertension; type 2 diabetes mellitus; dislipemia; obstructive sleep-apnoea; cardiovascular disease; insulin resistance.

The Neel's thrifty gene hypothesis¹ suggests that the human species has a very efficient capability to store energy as fat. In fact, this is a defence mechanism that has

Abbreviations: ADA, American Diabetes Association; AHI, apnea-hypopnea index; BMI, body mass index; CRP, Plasma C-reactive protein; CVD, cardiovascular disease; DM, Diabetes mellitus; FFA, Free fatty acids; HDL cholesterol, high-density lipoprotein cholesterol; IFG, Impaired fasting glucose; IGF-1, Insulin-like growth factor 1; IGFBP-3, IGF binding protein-3; IGT, Impaired glucose tolerance; IL-6, Interleukin-6; LDL cholesterol, low-density lipoprotein cholesterol; Lp (a), Lipoprotein (a); NEFA, nonesterified fatty acids; NHANES III, Third National Health and Nutrition Examination Survey; OHS, Obesity hypoventilation syndrome; OSA, Obstructive sleep apnea; PPAR- γ , peroxisome proliferator activated receptor- γ ; PREVENT, Prevention of Renal and Vascular End Stage Disease; RAAS, renin-angiotensin-aldosterone system; SHBG, sexual hormone binding protein; TNF- α , Tumor necrosis factor- α ; VLDL cholesterol, Very low-density lipoprotein cholesterol; WHO, World Health Organization; WHR, Waist to hip ratio; CNS, central nervous system; REM, rapid eye movement.

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facilitated the preservation of the species when our ancestor's life conditions were as hard as they were during the early years of the presence of human life on Earth. Notwithstanding, during human history, two main circumstances have occurred that transformed the ability to store energy as fat in a negative genetic characteristic for the species.

Firstly the succession of diverse famine periods during which individuals not genetically provided with this ability to store energy were not capable of surviving. Consequently, only those individuals who had this ability could continue the species. That this fact has been repeated four or five times throughout human history, has made it possible to select a human race with huge potential of storing energy and, therefore, developing obesity.

Nevertheless this has not been manifested until the other big revolution occurred: industrialization. During the last six or seven decades, we as humans have been developing machines that could help us save energy. The result is that nowadays our daily lives require minimal energy expenditure. From that point, the genetically determined energy storing capacity turns against us making us becoming obese, with type 2 diabetes, hypertensive, etc. This is how, what was initially a positive genetic trait, becomes a deleterious characteristic, leading to what the World Health Organization (WHO) has qualified as the 21st Century epidemic: obesity.

DEFINING AND MEASURING OBESITY

The body mass index

Obesity is a chronic disease consisting of the increase in body fat stores. Therefore, ideally, the definition of obesity should consider the amount of body fat. However, measuring body fat requires quite sophisticated methods that make population-based measure of body fat almost impossible to perform. Consequently, there are not precisely defined normal values of body fat. Thus, for practical reasons, obesity is measured by means of the Body Mass Index (BMI), a calculation taking into account the weight for a given height: $BMI = \text{Weight (kg)} / \text{height (m)}^2$. BMI highly correlates with total body fat and is very useful for epidemiological purposes. Based on the BMI and on its relationship with death from all causes, the WHO² has established different cut-off points enabling the classification of obesity (Table 1).

This WHO classification of obesity is universally accepted as a measure of obesity in adults, yet for childhood obesity, the use of the BMI may be somewhat confusing.

Table 1. Classification of adult obesity.

Classification	BMI (kg/m ²)	Risk of comorbidities
Normal range	18.5–24.9	Average
Overweight	≥25.0	
Preobesity	25.0–29.9	Increased
Obesity class I	30.00–34.9	Moderate
Obesity class II	35.00–39.9	Severe
Obesity class III	≥40.0	Very severe

Modified from Ref. 2.

Usually the percent of excess weight has been used to define the situation. A 120% of weight according to a weight for age and height tables has been considered as obesity. In line with these criteria, significant differences can be found on obesity prevalence in some European countries.

Due to its good correlation with fat mass, it might be desirable to use the BMI as a measure of obesity in children. The problem is that the BMI in children has normally wide variations in relation to age and race. Thus, what is normal in a specific society could be considered as pathologic in many other parts of the world. This is the main reason why the majority of paediatric associations had its own BMI percentile tables. This also explains the high variability we could find if we want to compare the prevalence of overweight or obesity among different countries. Normally a BMI above the 85th percentile is considered overweight while obesity is diagnosed when the BMI is over the 95th percentile of BMI according to the cut off points for this specific country.³

Recently efforts have been made to universalize these BMI cut off points, and the results have been released as a recent paper by Cole and co-workers.⁴ These tables can be used throughout the world, and will make it easier to define obesity both at individual and population levels. Using these new tables will probably lead to changes in the prevalence of obesity around the world. In fact, a recent survey in the U.K. has shown substantial changes in the prevalence of obesity using these new standards for BMI.

The waist circumference

Regarding the health risks related to obesity, we have to take into account not only the magnitude of obesity but also, and perhaps more relevant, the body fat distribution. There are two main types of obesity regarding the fat distribution pattern: android or central type obesity with the majority of fat depots located in the abdominal area, both subcutaneous and visceral, and gynoid or peripheral obesity in which the fat depots are mainly located subcutaneously in the lower body (hips and lower extremities). The difference between both types is fundamental, because the metabolic and cardiovascular complications of obesity are almost exclusively related to visceral fat depots.

Because of its high correlation with visceral adipose tissue⁵, a measure as simple as the waist circumference is a good way to assess cardiovascular risk. According to Mc Lean⁶, waist circumference cut off points can be established both for men and women, to assess cardiovascular risk. A waist girth over 88 cm for women and above 102 cm for men indicates a high cardiovascular risk and the need for action.

The waist-to-hip ratio

Although abandoned a little during the last five or seven years as a measure of fat distribution, the waist-to-hip ratio (WHR) is still a useful measure to be considered in obesity evaluation. Some experts consider that the hip measurement provides additional information about the gluteofemoral muscle mass and bone structure. In our opinion, in patients with severe and very severe forms of obesity (class II and III obesities in the WHO classification), with waist circumferences clearly beyond the upper risk limits, the WHR is the best way to evaluate the fat distribution pattern.

EPIDEMIOLOGY OF OBESITY

Due to its high worldwide prevalence, obesity is currently the most common metabolic disease in the world. The WHO estimates that more than one billion people are overweight and, of these, 300 million can be considered as obese, with a BMI above 30 kg/m^2 according its own BMI based classification of obesity. Actually, there is a great concern because the global figures of obesity are progressively increasing from an estimate of 200 million people affected in 1995 to the current 300 million, which is a 50% increase in only seven years. It is estimated that if no action is taken against this, these figures could double in 20 years. Moreover, this increase in obesity prevalence is a global trend, not only confined to affluent societies but also seen in emerging countries such as China.⁷

However, the prevalence of obesity varies widely among different continents and countries, ranging from almost one third of the whole population in Yugoslavia and Greece to a prevalence below 10% in the Netherlands and Switzerland. Obviously, beyond the genetic background there are some other influences, namely cultural and life style, which could explain these differences.

Figure 1 is an attempt to summarize the current figures about the prevalence of obesity in some countries that periodically undertake population-based health surveys.

Besides the high obesity prevalence, what really is concerning are the trends in obesity prevalence showing a progressive and non-stop rising tendency. Epidemiological studies comparing current and previous data clearly demonstrate this rising trend. In fact, in the U.S.A., the prevalence of adult obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) has doubled from 1986 to 2000, from 10% of the adult population to a current 20%. Also, during the same period of time, the prevalence of severe obesity quadrupled from 0.5 to 2% of the adult population.⁸ Similar growing trends are also seen in many other countries in the world.

Unfortunately, but not surprisingly, the prevalence of obesity is also increasing in childhood, mainly as a result of the dramatic changes in children's lifestyle (Figure 2). This increase in childhood obesity prevalence is not exclusive to fully developed countries. Countries like Mexico are also experiencing a rise in obesity prevalence in childhood. Mexican children 10 to 17 years of age have a current prevalence of obesity varying with age from 9.2 to 14.7% in boys and 6.8 to 10.6% in girls.⁹ These figures, even

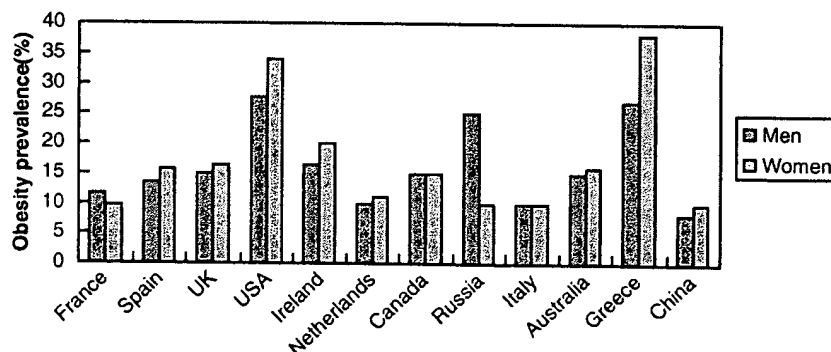


Figure 1. Prevalence of obesity in some countries undergoing epidemiological surveys. Modified from: International Obesity Task Force Report 2002. Accessible from: www.ietf.org.

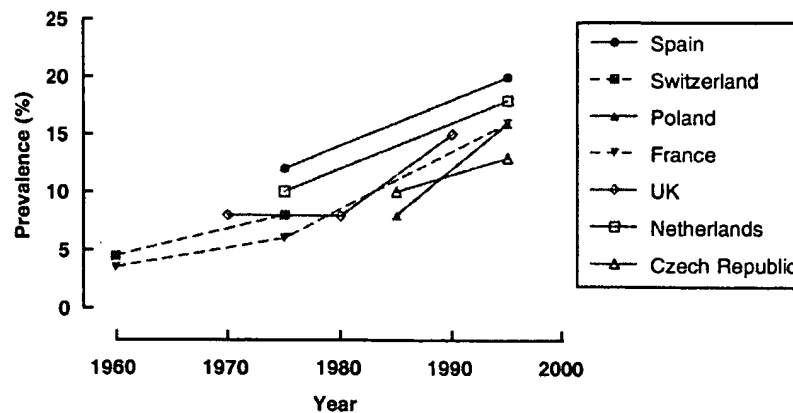


Figure 2. Trends in childhood obesity prevalence in some European countries. Modified from: International Obesity Task Force/European Association for the Study of Obesity, Obesity in Europe Report 2002.

though being approximately one half of those seen in the U.S.A., are really concerning given its rising trend. In Japan there is also a growing tendency in childhood obesity prevalence. However, this increase seems to be more important in small rural towns, with the girls living in metropolitan areas not being a part of this phenomenon.¹⁰ These differences between trends in rural and urban areas are important when considering obesity prevention or intervention policies.

The fact of being obese during adolescence is of great importance with respect to the risk of adult obesity. The results of the study of Laitinen et al¹¹ demonstrates clearly how the BMI at 14 years of age is the best predictor of adult obesity.

HEALTH CONSEQUENCES OF OBESITY

The importance of obesity comes from being a life-threatening condition and because it is a genuine risk for many non-communicable diseases.

In a prospective study done on a cohort of more than one million adults in the United States, Calle et al¹², found in healthy people who had never smoked, a relative risk of death of 2.58 and 2.00 for men and women, respectively, among those with the highest BMI as compared with those with BMI of 23.5 to 24.9. Data from the Framingham Heart Study¹³ show a significant reduction in life expectancy among nonsmoking obese people in comparison with those also nonsmokers at normal BMI range (18.5–24.9 kg/m²). Such reduction accounts for 7.1 years for females and 5.9 years for males (Figure 3). Anyway, it seems that the effect of BMI on mortality is age-dependent, so the relative risk associated with greater BMI declines with age.¹⁴

Besides being a shortening life factor, obesity and precisely central type obesity, is commonly associated with many other diseases mainly in the cardiovascular and metabolic area. In fact, nowadays obesity is considered a cardiovascular risk factor *per se*, independently of its demonstrated capability of exacerbating other known risk factors. Thus, central type obesity is often associated with high blood pressure, ischaemic heart disease, stroke, type 2 diabetes and dyslipidemia. Apart from these metabolic and cardiovascular disturbances, obese people are frequently suffering from

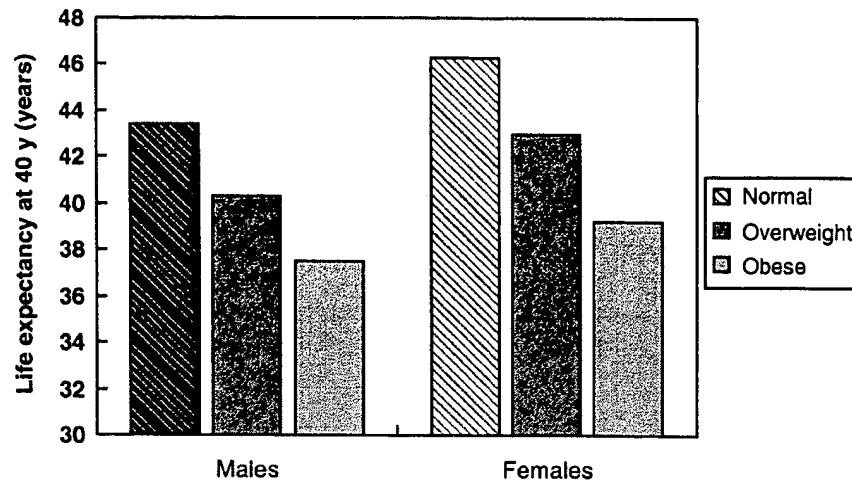


Figure 3. Life expectancy at 40 years in obese people is reduced by 7 years in women and by 6 years in men. Modified from Ref. 13

joint diseases and respiratory disorders such as obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS).

Diseases associated with obesity could arise from two mechanisms: from the metabolic changes associated with excess fat, as type 2 diabetes mellitus and cardiovascular disease, or from the increased fat mass itself, as it is clearly the case for joint diseases.

The adipose tissue stores excess energy in the form of lipids but, in recent years, it has been demonstrated that the adipose tissue behaves as an endocrine organ, the fat cell acting as a type of endocrine cell. Central type obesity leads to an imbalanced production of several metabolic products, hormones and cytokines (adipocytokines), with a variety of local, peripheral and central effects. These fat cell-derived products include leptin, resistin, adiponectin, free fatty acids (FFA), tumor necrosis factor- α (TNF- α) and interleukin 6 (IL-6).¹⁵

In summary, obesity can affect almost all organs and tissues of the body, from the brain to the lower extremities, causing a multitude of clinical problems. In the forthcoming sections we will go through the most clinically relevant ones.

Insulin resistance and type 2 diabetes mellitus

The relationship between obesity and insulin resistance applies to all ethnic groups and the full range of body weights. Insulin is a regulator of the adipocyte biology and adipocytes are one of the cells of the body with a higher response to insulin. Insulin fosters the differentiation of preadipocytes to adipocytes, stimulates lipogenesis, and inhibits lipolysis.¹⁶

Insulin resistance is defined as the decreased effect of insulin on glucose uptake, metabolism and storage. There is a diminished insulin-stimulated glucose uptake in skeletal muscle and adipose tissue, and impairment in the suppression of hepatic glucose output. These defects may be determined by impaired insulin signaling or by the down-regulation of the glucose transporter, GLUT4. In relation to the signaling defects

in obesity, it is important to consider that the initial signal for insulin action is the activation of the tyrosine kinase of the insulin receptor, which determines the phosphorylation of several tyrosine residues. In muscle and adipose tissue of obese humans and rodents there is an increased expression and/or activity of several protein tyrosine phosphatases, which dephosphorylate and terminate signaling propagated through tyrosine phosphorylation.¹⁷ Additionally, a reduction in the expression of several insulin signaling molecules has been described in skeletal muscle in morbid obesity. In the case of GLUT4 expression, it seems to be normal in skeletal muscle of obese and diabetic subjects and defective glucose transport appears to be due to impairment of translocation, docking, or fusion of GLUT4-containing vesicles with the plasma membrane.¹⁸

There are also potential mechanisms linking intramuscular lipids to skeletal muscle insulin resistance.¹⁹ In this sense, it is important to consider two different pools of lipid storage in skeletal muscle, extramyocellular lipids (adipocytes located between muscle fibers), and intramyocellular lipids (cytosolic triglycerides) located within the muscle cells. An interesting work developed by Bachmann et al²⁰ studying twelve healthy male subjects that underwent a six hour hyperinsulinemic euglycemic glucose clamp with concomitant infusion of lipid plus heparin, suggests a functional relationship between increased intramyocellular lipids, quantified by ¹H-magnetic resonance spectroscopy, and reduced insulin sensitivity. On the other hand, it seems that adiponectin promotes lipid oxidation resulting in lower intracellular lipid content in human muscle.²¹

Intra-abdominal fat depots are much more strongly linked to insulin resistance than subcutaneous fat depots. Then, subjects with central fat distribution are more prone to insulin resistance. Although it is possible that an unknown factor produces both insulin resistance and central obesity, the leading hypothesis is that adipocytokines have a major effect on insulin sensitivity.

Obesity is accompanied by the production of several cytokines that decrease insulin sensitivity in liver and skeletal muscle. TNF- α has paracrine effects on adipose cells, and reduces insulin action in skeletal muscle.²² Free fatty acids (FFA) released from the more lipolytically active intraabdominal adipocytes, increase insulin resistance in liver and skeletal muscle through mechanisms affecting the intracellular insulin signalling cascade.²³ On the contrary, adiponectin, a true hormone acting through receptors in insulin target tissues as skeletal muscle and liver, improves insulin sensitivity by enhancing intracellular insulin signalling.²⁴ A reduced serum adiponectin has been reported in obesity.^{25,26} However, other studies have shown that it is the subcutaneous adipose secretion rate of adiponectin which is reduced in obese compared with non-obese subjects, but not serum levels, which are non-significantly different from those of non-obese patients. The fact that insulin resistant individuals have lower values of both adipose secretion rate and serum concentration than subjects with high insulin sensitivity would suggest that the degree of hypoadiponectinemia in obesity is related to insulin resistance rather than body fat.²⁷

The National Cholesterol Education Program Adult Treatment Panel III has established that the syndrome of insulin resistance exists when three of the five following criteria are abnormal: waist circumference >102 cm (>40 in.) in men and >88 cm (>35 in.) in women; HDL cholesterol <40 mg/dl in men and <50 mg/dl in women; triglycerides \geq 150 mg/dl; fasting glucose \geq 110 mg/dl; and blood pressure (systolic and diastolic blood pressure) \geq 130/ \geq 85 mm/Hg.²⁸ A prothrombotic and proinflammatory state is also characteristic of the insulin resistance syndrome. In fact, plasma C-reactive protein (CRP) levels, a liver acute phase

protein largely regulated by circulating level of interleukin-6 and considered to be a marker of inflammatory states, are strongly associated with obesity and obesity-related disorders, including insulin resistance, diabetes mellitus, and dyslipemia.²⁹ In fact, obesity is now considered to be a low grade inflammatory state. An inverse relationship was observed between CRP and adiponectin in both plasma and adipose tissue.³⁰

Type 2 diabetes mellitus (DM), accounting for the 90–95% of those persons with diabetes, and previously known as non-insulin dependent diabetes or adult-onset diabetes, refers to individuals who have insulin resistance and insulin levels that frequently appear normal or elevated but are insufficient to compensate for insulin resistance, resulting in high blood glucose levels. Most patients with this form of diabetes are obese, and obesity has been recognized as a significant risk factor for the development of type 2 DM. Although not all obese individuals develop type 2 DM, the increase in the prevalence of obesity has been associated with an increase in its prevalence³¹, and in the Nurse's Health Study overweight or obesity was the most important predictive factor.³² The duration of obesity has also been considered positively associated as well as the fat distribution pattern. Again, central obesity is found to be a major risk factor independently of the severity of obesity.³³ In the last decade there is increasing evidence suggesting a positive association between low birth weight and impaired glucose tolerance, and even type 2 DM in adulthood.³⁴ Bhargava et al³⁵ have reported, studying more than 1400 adults in India, that low body weight and thinness at one to two years of age were associated with impaired glucose tolerance and diabetes in adulthood. This low body-mass index was followed by an early adiposity rebound (the age after infancy when body mass starts to rise) and an accelerated weight increase afterwards.

Subjects who develop type 2 diabetes experience progressive deterioration of glucose tolerance over time, progressing from normoglucaemia to impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), and finally overt diabetes that appears when decreased insulin secretory capacity due to β -cell dysfunction appear after years of insulin resistance.³⁶ Patients with IFG and/or IGT are now referred to as having 'pre-diabetes', indicating the high risk of future diabetes as well as cardiovascular disease. According to the American Diabetes Association (ADA), the IFG is defined as a fasting plasma glucose (FPG) of 100–125 mg/dl (5.6–6.9 mmol/l) and IGT as a 2-hour post-load glucose (after 75 g of glucose) of 140–199 mg/dl (7.8–11.1 mmol/l).³⁷ Criteria for the diagnosis of diabetes mellitus are presented in Table 2.

Dyslipemia

Obesity-associated dyslipemia plays a crucial role in the development of atherosclerosis and cardiovascular disease in obese subjects, because all the elements of the dyslipemia normally associated with this disease have been shown to be atherogenic.

Obesity, mainly of central fat distribution, is associated with increases in plasma triglycerides, and decreases in HDL cholesterol. In fact, when adjusting for BMI, patients with a higher WHR seem to have higher triglycerides levels and lower HDL cholesterol levels.³⁸ The effect of obesity on LDL cholesterol levels is not so clear. To this respect, obese young men have LDL concentrations higher than those of normal weight, but in middle age and older men, only minimal differences occurred.³⁹ Interestingly, a change in LDL composition occurs in obese individuals whose LDL particles are smaller and more dense, increasing the risk of cardiovascular disease in individuals with this kind of LDL particles than in those with large LDL particles for the same level of total

Table 2. Categories of abnormalities in glucose metabolism according to the American Diabetes Association criteria (2004)

Normoglycemia	IFG/IGT	Type 2 diabetes mellitus ^a
<ul style="list-style-type: none"> • FPG < 100 mg/dl (5.6 mmol/l) • 2-hours postload glucose < 140 mg/dl (7.8 mmol/l) 	<p>IFG:</p> <ul style="list-style-type: none"> • FPG 100–125 mg/dl (5.6–6.9 mmol/l) <p>IGT:</p> <ul style="list-style-type: none"> • 2-hours postload glucose ≥ 140 mg/dl (7.8 mmol/l) and < 200 mg/dl (11.1 mmol/l) 	<ul style="list-style-type: none"> • FPG ≥ 126 mg/dl (7.0 mmol/l) or • 2-hours postload glucose ≥ 200 mg/dl (11.1 mmol/l) or • Symptoms of diabetes plus casual FPG ≥ 200 mg/dl (11.1 mmol/l)

FPG: fasting plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance

^a In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

cholesterol and, again, associated with a central distribution of the fat.⁴⁰ The reduced diameter of these particles favours their movement through the endothelial fenestrations, and their location in the subendothelial space determining the formation of the plaque. Small LDL particle concentrations and triglyceride levels are positively correlated, because the formation of these LDL molecules depends on the metabolism of VLDL particles.

This obesity-associated pattern of dyslipidemia (high triglyceride levels, low HDL concentrations, and dense and small LDL particles) is related to insulin resistance. The presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated BMI.

Lipoprotein a (Lp(a)) is known to be an independent risk factor for coronary, cerebrovascular and peripheral vascular disease when its serum concentration exceeds 30 mg/dl. Structurally Lp(a) is very similar to LDL cholesterol and plasminogen and its levels are relatively constant throughout life. Higher than normal serum concentrations of Lp(a) are commonly seen in central type obesity.⁴¹

Simple variables, such as triglyceride levels and waist circumference can be used to identify individuals with a cluster of new metabolic risk factors for cardiovascular disease, such as hyperapoprotein B, small dense LDL levels and hypertriglyceridemia. It is the known concept of the 'hypertriglyceridemic waist'.⁴²

The primary defect in lipid metabolism in obesity seems to be the overproduction of VLDL by the liver. In the insulin resistant state, normally present in these patients, there is a decreased ability of insulin to suppress hepatic glucose output and the release of nonesterified fatty acids (NEFA) from adipose tissue. These events play an important role in hepatic VLDL production. Besides this increased synthesis, there is a decreased clearance of triglyceride-rich lipoproteins in the circulation due to decreased lipoprotein lipase activity.⁴³ This impaired triglyceride lipolysis leads to reduced HDL concentrations by decreasing the transfer of apolipoproteins and phospholipids from triglycerides to the HDL compartment. Another characteristic of obesity is the impairment in LDL receptor activity, the most important point of clearance from

the circulation of VLDL particles. A negative correlation between lipoprotein lipase activity and the clearance rate of HDL has been found.⁴⁴ In insulin-resistant subjects, a decrease in HDL particles occurs, especially in the larger HDL2 in comparison with the smaller HDL3, making this change more atherogenic.

Hyperuricemia

Hyperuricemia is frequently observed in obese subjects due to the overproduction of uric acid and its impaired renal excretion. Matsuura et al⁴⁵, reported that purine synthesis and the overproduction of uric acid could be linked to fatty acid synthesis by the liver. On the other hand, hyperinsulinemia has been proposed as a contributing factor to increased levels of uric acid in obesity, due to its renal effect resulting in diminished clearance of urate. The amelioration of insulin resistance by either a low-energy diet or insulin-sensitizing agents decreases the serum uric acid concentration in overweight hypertensive patients.⁴⁶

Cardiovascular disease

Obese subjects have increased risk of cardiovascular disease (CVD), and this is true especially for the abdominal or central type obesity. Obese individuals with central fat distribution are at higher risk for heart disease than those with peripheral type of obesity. Classically, weight cycling has been linked to a higher cardiovascular risk. However, it appears that weight cycling in obese subjects of both genders is not associated with cardiovascular risk factors in an independent manner⁴⁷ and in middle-aged men does not directly increase the risk of death.

The connection between obesity and CVD is not simple.⁴⁸ The atherosclerotic process is apparently regulated by inflammatory mechanisms⁴⁹ and systemic inflammation has been linked to insulin resistance in a large number of human population studies.

Hypertension

Among all the obesity related comorbidities, high blood pressure is, probably, the most well known. There is a huge amount of epidemiologic evidence demonstrating this relationship. In the U. S. A., data from the third National Health and Nutrition Examination Survey (NHANES III) clearly demonstrate a positive and linear association between the value of the BMI and the percentage of people with arterial hypertension. The Health Professionals Follow-up Study⁵⁰ shows that among obese men ($\text{BMI} \geq 30 \text{ kg/m}^2$) around 35% are hypertensive. Also, in women there is a strong relationship between obesity and hypertension. In the Nurse's Health Study it is clearly seen that, women with a BMI over 30 kg/m^2 have a four-fold increase in relative risk of having high blood pressure in comparison with those with a BMI of 21 kg/m^2 .⁵¹

Whereas the epidemiological evidences are overwhelming, the physiopathological mechanisms linking obesity and hypertension are not fully known.

Two haemodynamic disturbances are commonly seen in obesity-associated hypertension: increase of intravascular volume, and an 'abnormally normal' peripheral vascular resistance unable to respond correctly to the enhanced intravascular volume. The primary defect leading to the increase in intravascular volume should be some renal disturbance producing a change in the pressor natriuresis. In fact, obesity-hypertension shows an increase in sodium retention. Moreover, as demonstrated in animal models⁵²,

increased sympathetic activity is commonly found in obese hypertensive humans, which could explain, at least in part, the haemodynamic disturbances.

There might exist common mechanisms that could be, at the same time, responsible for the abnormal sodium retention, the lack of adaptation to the increase of intravascular volume and for the increase of sympathetic activity; the true nature of these mechanisms has not been fully elucidated. Some hormonal systems could have a major role. There have been a lot of speculations about the role of hyperinsulinaemia and insulin resistance but it is clear that hyperinsulinaemia is not the cause of the hypertension in the obese.⁵³

Leptin, a 167 amino acid peptide hormone, might be also potentially involved in the hypertension of the obese. Nevertheless, whereas there is some evidence of its causal role in laboratory animals, the results of the studies performed in humans are somewhat confusing, and therefore it is not possible by any means, to ascribe to leptin any causal role in obesity hypertension.⁵⁴

The renin-angiotensin-aldosterone system (RAAS) probably has a key role in obesity hypertension. The RAAS seems to be hyperactivated in obesity, in spite of the increase of intravascular volume and sodium retention. Engeli and Sharma have demonstrated a direct association between plasma leptin and angiotensin levels suggesting that adipose tissue may contribute to the plasma angiotensin level.⁵⁵

In recent years it has become manifest that adipose tissue possesses a local RAAS which is supposed to play an important role in adipose tissue functioning. For instance, angiotensin II is involved in the metabolism and differentiation of adipose tissue and in lipid storage. In fact, in central obesity, a positive relation between the waist-to-hip ratio (WHR) and the expression of angiotensinogen mRNA in the omentum has been found.⁵⁶ Recently, angiotensinogen production by human cultured fat cells has been shown, though not having any relationship with the BMI.⁵⁷

However, as not all the obese are hypertensive and the obesity-hypertension association is commonly seen within families, a genetic predisposition is likely to be necessary to express these disturbances.

Heart disease

Obesity is associated with several heart abnormalities. In a study of the American population, there was a significant increase in the prevalence of heart disease, diabetes, hypertension and hypercholesterolemia with increasing body weight in all gender, racial and socioeconomic groups.⁵⁸

Obesity is associated with accelerated coronary atherosclerosis and long-term longitudinal studies demonstrate that obesity predicts coronary atherosclerosis in an independent manner. The risk for developing coronary artery disease is increased 3.3-fold in American women with a BMI over 29 kg/m², in comparison with women with a BMI below 21 kg/m².⁵⁹ Moreover, a WHR of ≥ 0.92 is associated with a 3-fold increased risk of coronary heart disease.⁶⁰ IL-6, a cytokine produced by adipose tissue, seems to play a key role in the development of coronary heart disease associated with obesity through different metabolic, endothelial and procoagulant mechanisms.⁶¹

Left ventricular hypertrophy is frequent in obesity, and is not just related to concomitant hypertension: increases in stroke volume, cardiac output and diastolic dysfunction are seen in obese subjects without hypertension. The changes affecting the left ventricle have been related to sudden deaths in these patients.

Not only the left ventricle but also the right ventricle presents some changes. As a consequence of left ventricular dysfunction or the coexistence of OSA and/or obesity

hypoventilation syndrome, *cor pulmonale* can occur. Therefore, for all these reasons heart failure in obesity is frequently biventricular.

Obesity can also be the cause of arrhythmias, and the prolonged QT interval also seen in obesity might be a predisposing factor for sudden death.⁶²

Also, in patients with morbid obesity, we have demonstrated that although the cardiopulmonary capacity appears to be normal, the exercise capacity is significantly reduced, as compared to control subjects.⁶³

Stroke

The association between obesity and stroke remains controversial, although most studies have shown a positive relation. In a prospective study of 21 414 US male physicians participating in the Physicians' Health Study, increasing BMI is associated with a rise in the risk of total, ischemic and hemorrhagic stroke independently of the presence of hypertension, diabetes and dyslipemia (Figure 4). BMI is also inversely associated with the severity of fatal hemorrhagic stroke, particularly subarachnoid hemorrhage.⁶⁴ Another prospective and interesting study done in 234 863 Korean men has demonstrated that BMI is a risk factor for both ischemic and haemorrhagic stroke.⁶⁵ Subarachnoid haemorrhage showed no significant trend related with BMI. Other studies have underlined abdominal obesity as an independent risk factor for ischaemic stroke in all race-ethnic groups, being a stronger risk factor than BMI and with a greater effect among young subjects.⁶⁶

Plasma leptin has been considered a risk factor for first-ever haemorrhagic but not ischaemic stroke, in an independent manner of other risk markers for CVD.⁶⁷ If we consider that most obese people have leptin resistance with high levels of plasma leptin, we could speculate that leptin might be the link between obesity and haemorrhagic stroke.

Gallbladder disease

Besides hepatic steatosis, a topic deserving a chapter in this issue, cholelithiasis is the primary hepatobiliary pathology associated with obesity. Obese women have at least twice the risk of gallbladder disease as compared with normal weight women. The risk of having gallbladder disease is positively associated with the BMI. In men, this association has been reported less consistently than in women. In a population-based study, central obesity was related to gallbladder disease in both sexes.⁶⁸

Csendes et al⁶⁹ reported in a prospective study of 125 obese patients a high frequency of gallstones (30.4%). The explanation for the cholelithiasis seems to be the higher excretion of cholesterol through the bile in obese patients, favoured by high plasma levels of cholesterol and triglycerides frequently found in obesity. This high concentration in relation to bile acids and phospholipids increases the probability of precipitation of cholesterol gallstones in the gallbladder. From a functional point of view, an increased gallbladder volume and apparently slower gallbladder emptying has been described.

Locomotor system

There are functional locomotor limitations in obese women.⁷⁰ They have flexibility troubles and frequently pain in performing tasks at floor level such as picking things up.

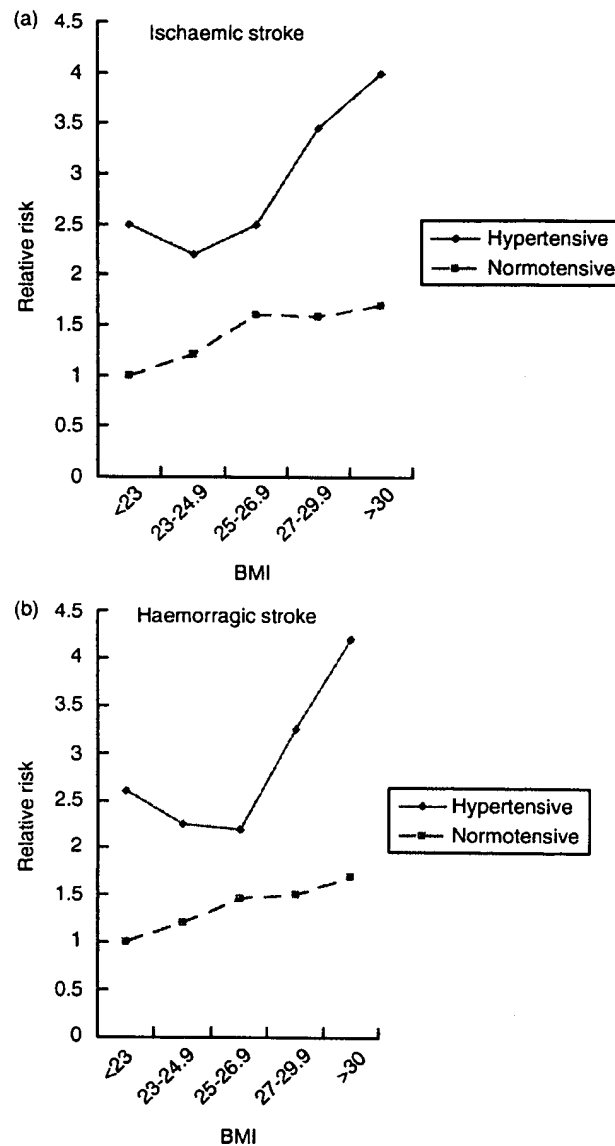


Figure 4. The association of obesity and the risk of ischaemic (panel a) and haemorrhagic (panel b) stroke.

squatting or kneeling. They also move more slowly, and experience more exertion than the control population.

On the other hand, osteoarthritis and other joint problems are more frequent in obese subjects. The first National Health and Nutrition Examination Survey showed

that women with a BMI between 30–35 kg/m² had nearly four times the risk of arthritis of the knee than women with a BMI under 25 kg/m².⁷¹ In fact, several case-control studies have demonstrated a strong association between knee osteoarthritis and obesity and in the Framingham study high BMI predicted development of the disease.⁷² A population-based case-control study in three districts of England has shown that a large proportion of severe knee osteoarthritis is attributable to obesity, being this risk especially high among obese subjects with other risks factors as generalized osteoarthritis and surgery or knee injury.⁷³

Arthritis develops as a consequence of trauma associated with the excess of body weight in joints such as the knees and the ankles. However, the osteoarthritis prevalence in non-weight-bearing joints would suggest an alteration of the cartilage and bone metabolism, occurring independently of weight bearing.

Obesity-related kidney disease

Obesity is related also to kidney disease. The renal effects of obesity include both structural and functional changes. Both glomerulomegaly and focal segmental glomerulosclerosis (Figure 5) have been associated with obesity, not only massive obesity but also class I and II obesity. In relation to functional adaptations, increased glomerular filtration rate, increased renal blood flow and renal hypertrophy are considered to be the most relevant. Clinically, the presentation of obesity-related glomerulopathy is nephrotic or sub-nephrotic range proteinuria and renal insufficiency in 44% of cases. In 45% of cases, biopsies show focal glomerular basement membrane thickening or focal mesangial sclerosis, as seen in early diabetic nephropathy.⁷⁴

Indeed, an increased BMI has been associated with a potential marker of cardiovascular disease such as microalbuminuria, seen mainly in subjects with hypertension.⁷⁵ In a subanalysis of the PREVENT (Prevention of Renal and Vascular End Stage Disease) study, the prevalence of microalbuminuria (30–300 mg/24 hours) in men increased from 9.5% in those with normal body weight, to 18.3% in overweight subjects, and to 29.3% in individuals with obesity. These percentages in women were 6.6, 9.2 and 16%, respectively.⁷⁶

Obesity may have similar effects as diabetes on the kidney, with an initial phase of glomerular hyperfiltration followed by microalbuminuria, with this phase followed by a progressive fall in glomerular filtration rate and a further rise in urinary albumin excretion with the development of proteinuria and, sometimes, end-stage renal failure.⁷⁷ This hypothesis suggesting that glomerular hyperfiltration underlies the pathogenesis of glomerulopathy in obesity is reinforced by experiments in obese Zucker rats.⁷⁸

The exact mechanism behind the obesity-related kidney damage is not known. Haemorheologic alterations such as higher blood viscosity, hyperfibrinogenemia, and lower erythrocyte deformability values have been related to proteinuria in patients with central obesity.⁷⁹ Hyperleptinaemia and insulin resistance could be some of the other involved mechanisms, since insulin resistance induces intraglomerular hypertension as well as mesangial hypertrophy.⁷⁴ Increased serum glucagon concentration has been considered another risk factor for the development of glomerular hyperfiltration in central obesity. On the other hand, the inflammatory changes in the setting of obesity could also be another of the mediators of renal disease, since higher CRP levels are also associated with a higher relative risk of impaired glomerular filtration.⁸⁰ In a subsample of participants in NHANES III who were 20 years of age and older, the percentage of

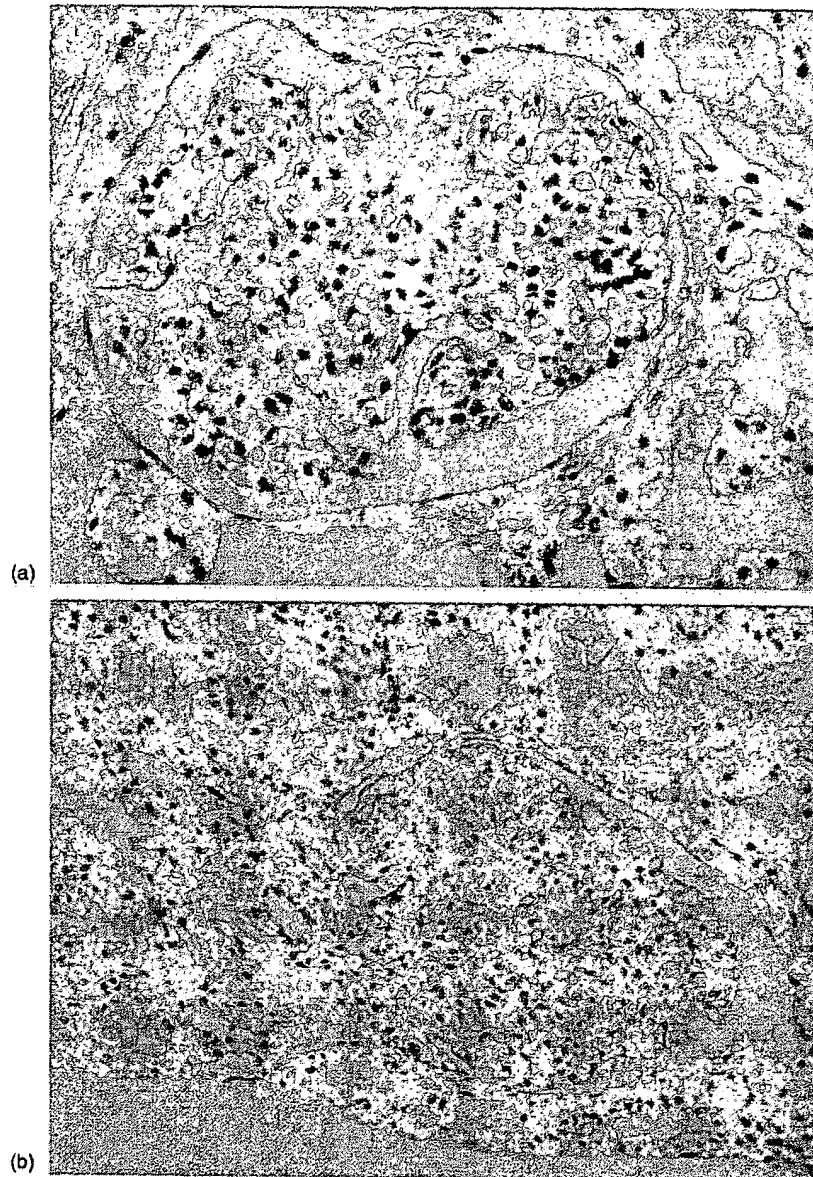


Figure 5. (a) Lesions of focal segmental glomerulosclerosis in a patient with severe obesity (b) Glomerulomegaly from another severe-obese non-diabetic patient.

persons with chronic kidney disease or microalbuminuria was significantly higher among those with the metabolic syndrome, compared with those without it. A low HDL cholesterol level and abdominal obesity were significantly associated with an increased prevalence of chronic kidney disease.

Obesity and cancer

There is a growing body of evidence that obesity has also some kind of cause-and-effect relationship with many types of cancers. Given the global rising trend in obesity prevalence, even a small added risk of cancer due to obesity should be a major concern. In the U.S.A., an increase in the relative risk of dying from cancer has a clear positive association with the BMI both for men and women. Assigning the risk 1 to people with a normal BMI (18.5–24.9), those with obesity class II have a 1.3-fold relative risk, whereas those with a BMI ≥ 40 kg/m² have a relative risk higher than 1.5.⁸¹

The study by Calle et al⁸² is a prospective cohort investigation done on a very large population sample (more than 900 000 U.S.A. adults), with a follow up of 16 years. The authors examined the relation between the BMI in 1982 and the risk of death from all cancers and from different types of cancer, calculating also the proportion of all deaths from cancer that can be attributable to overweight and obesity in the U.S.A. The results of the study clearly show that being obese increases the risk of death from all types of cancer. Regarding the mortality from specific types of cancer, people in the highest category of BMI have a significantly higher risk of dying from almost all types of cancer than those in the normal BMI range (18.5–24.9 kg/m²). For women, the risk of death from endometrial cancer is 6.25-fold higher in obese women in comparison with those with a normal BMI. Obese men have a relative risk of death from liver cancer of 4.52 compared with non obese ones. The influence of fat distribution, body composition and weight change or weight cycling was, unfortunately, not analysed in this study.

A similar population-based study done in Canada also showed a strong direct association between obesity and cancer.⁸³ The authors found that, overall, obesity accounted for 7.7% of all cancers in Canada, providing further support for the positive association of obesity with cancers of the kidney, colon, rectum, breast (in postmenopausal women), ovary, pancreas and prostate. The occurrence of endometrial cancer was not reported in this study.

In women the relationship between BMI and breast cancer seems to be age dependent. Thus, premenopausal obese women might have a decreased risk of breast cancer as compared with those premenopausal women within the normal range BMI.⁸⁴

Thus, there is a huge amount of epidemiological evidence about the relationship of obesity with cancer. Less clear are the mechanisms through which obesity predisposes to cancer. One of the factors commonly may involve estrogens: obesity is commonly associated with elevated free circulating estrogens level due both to increased production from adipose tissue and to a decreased sexual hormone binding protein (SHBP).

Recently Moore et al⁸⁵, in a cohort of patients from the Framingham Study, found that the degree of central obesity, measured by waist circumference, is a stronger predictor of colon cancer risk than is BMI. Thus, central fat distribution could be involved in the increased cancer risk of obese people. Central obesity is associated with high levels of insulin-like growth factor I (IGF-I) which is capable of inhibiting apoptosis and stimulates cell proliferation. IGF-I is associated with diverse types of cancer (breast, ovarian, colorectal, lung, prostate and bladder).⁸⁶

Another factor related to IGF-I and potentially involved in the obesity-associated cancer risk, is IGF-I binding protein 3 (IGFBP-3). IGFBP-3 normally binds to IGF-I, impeding it entering tissues and binding to its receptors. High levels of IGFBP-3 would protect against cancer.

Adiponectin, an hormone produced by adipose cells with insulin sensitizing properties, has been shown to be inversely related to the degree of obesity and insulin resistance. Adiponectin is also involved in cancer risk. The group of Trichopoulos recently reported an inverse association between plasma adiponectin levels and the risk of endometrial⁸⁷ and breast⁸⁸ cancers, the latter being found only in postmenopausal women.

Some genes could also be involved in the association of obesity and cancers. This is the case of the peroxisome proliferator activated receptor- γ (PPAR- γ) which might be involved in prostate cancer.⁸⁹

Respiratory disease

Two of the most common respiratory disturbances found in obesity are: obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS). In severe cases, both diseases can constitute a real threat for the patient's life.

Obstructive sleep apnea

The most well known although little studied respiratory disease associated with obesity is OSA. The prevalence of OSA in the general population is highly variable, from 25 to 58% of men and 10 to 37% of women, depending on the race and the geographic area studied.⁹⁰ But symptomatic OSA, with daytime somnolence, is supposed to affect only 4 and 2% of middle age men and women respectively.⁹¹ This means that the majority of patients suffering from OSA is not diagnosed and therefore not treated, which is potentially harmful.

The association of obesity with OSA is strong, although very variable among the published studies. It is known that around 70% of individuals with OSA are obese and that the prevalence of OSA among obese people is approximately 40%.⁹² In grade III obesity, OSA is almost the rule.⁹³

The events characterizing OSA are the apneas caused by the occlusion of the upper airway. The immediate consequence of the apnea is a decrease in the oxygen concentration which is responsible of the arousal, bringing the patient to a lighter sleep state, making it possible to restore the airflow and, consequently, return the oxygen concentration to normal levels. Nevertheless the arousal is transient and the sequence of events is repeated again and again during the sleep time.

The severity of OSA is defined by the apnea-hypopnea index (AHI) which is the number of apnea or hypopnea episodes per hour. Currently, it is considered that an AHI above 5 is diagnostic of OSA and severe OSA is diagnosed when the AHI is greater than 20.⁹⁴

The cause of OSA in obesity is related both to anatomic and functional characteristics of the pharyngeal muscular structures and to the state of central nervous system (CNS) activity. Obese individuals have a narrowing of the upper airway due to an extrinsic soft tissue enlargement because of fat deposits in the posterolateral oropharyngeal area. In fact, BMI, neck circumference and the size of the retroglottal space are the main determinants of OSA. Patients with central type obesity are more prone to have OSA because of their fat accumulation pattern (visceral and trunk). Waist circumference and visceral fat area correlates with the severity of OSA, more so than BMI.

Besides the anatomical changes that may occur in the oropharyngeal region of the obese, the central nervous system (CNS) also plays a crucial role in the pathogenesis of OSA. The decrease of the CNS activity during the rapid eye movement (REM) phase of

sleep results in a decrease in the diaphragmatic and oropharyngeal muscle activity which facilitates the airway collapse.

Obesity-hypoventilation syndrome

The other respiratory disturbance associated with obesity is the poorly known obesity-hypoventilation syndrome (OHS). This syndrome is characterized by daytime hypercapnia and severe hypoxemia (arterial partial oxygen pressure <70 mm Hg) in the absence of lung or neuromuscular disease. Associated clinical features of the syndrome include *cor pulmonale*, cyanosis and daytime somnolence. OHS is poorly understood, and why some obese persons hypoventilate and others do not remains unknown. The disorder seems to be the result of interaction of genetic factors plus an increased load on the respiratory system.

SUMMARY

In summary, obesity is considered to be the most prevalent metabolic disease in the world. As a result, of civilization there have been important changes in lifestyle leading to a progressive decline in the necessity of physical activity. The consequence is a rising trend in its prevalence worldwide, not only in adults but also, and more concerning, in childhood.

This increase in obesity prevalence has important consequences in terms of public health because of the concomitant increase in the multiple non communicable diseases associated with obesity. These include metabolic disturbances such as type 2 DM, dislipemia and hiperuricemia, as well as cardiovascular diseases, being hypertension, ischaemic heart disease and stroke, the more common. Nevertheless, obesity and particularly central type obesity can affect almost every organ and system of the body. Respiratory disturbances, often misdiagnosed in obese people, can severely affect their health and quality of life. This is the case for obesity-hypoventilation syndrome and the better known obstructive sleep apnea syndrome.

We are confronting a real obesity epidemic and major efforts should be driven towards a better understanding about the causes of obesity so that we can find effective and safe tools to treat obese patients. In parallel to that it is imperative the implementation of preventive policies in order to stop the rising trend in obesity prevalence. Otherwise in a few decades the world will be obese with a tremendous impact in terms of public health and economic costs.

Practice points

- currently, there are 300 million obese people in the World, and this figure could double by year 2025
- central type obesity is commonly associated with an increased risk of cancer and metabolic, cardiovascular and respiratory comorbidities
- the obesity-associated pattern of dyslipemia includes high triglyceride levels, low HDL cholesterol concentrations, and dense and small LDL particles
- obesity, and more strongly central type obesity, is linked to insulin resistance and type 2 diabetes mellitus

Research agenda

- the role of adipose tissue as an endocrine organ is opening new perspectives in obesity research
- the intimate relationship between obesity and cardiovascular disease needs to be completely elucidated
- more research on the relationships of obesity and cancer risk is needed

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